# Barbara McClintock, 1902-1992

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On Wednesday, September 2, 1992, Barbara McClintock died peacefully. Just two and one-half months earlier, she had celebrated her 90th birthday at Cold Spring Harbor Laboratory with a group of friends and colleagues who had contributed to a festschrift in her honor [1].

McClintock was one of the outstanding figures in modern science. Her 69 year career was an integral part of the genetic revolution that is still transforming our understanding of life. From her student days at Cornell University (BS 1923, PhD 1927), where she joined Emerson's group as it was pioneering maize cytogenetics, to her last years at Cold Spring Harbor, where she became a revered source of wisdom about all aspects of biology, McClintock continually directed others towards new intellectual frontiers. Following six years of postdoctoral work at Cornell and an eye-opening fellowship in Berlin, she took an assistant professorship in 1936 at the University of Missouri where she could analyze Stadler's X-irradiated maize stocks. Frustrated by the treatment she received there as a woman doing independent science, McClintock left Missouri in 1941, and in 1942 she obtained a staff position with the Carnegie Institution of Washington genetics group at Cold Spring Harbor. She remained at Cold Spring Harbor the rest of her life, although she also did important work on maize and *Neurospora* at Cal Tech and Stanford, taught periodically at Cornell, and directed a Rockefeller Foundation project using cytogenetics to trace the races of maize throughout the Americas [2].

McClintock's career included some of the seminal discoveries elucidating the physical structure of the genome and was recognized by numerous honors, including the 1983 Nobel Prize for Medicine. Early in her career, she worked out the methods for visualizing maize chromosomes, and she was instrumental in establishing that chromosomes are the physical carriers of genetic linkage groups. Her 1931 paper with her student Harriet Creighton, 'A correlation of cytological and genetical crossing-over in *Zea mays*' [3], remains one of the classics of genetics. She discovered the nucleolus organizer region [4], and her work on chromosome mechanics formed the basis for significant portions of genetics textbooks in the pre-DNA era [5]. In 1932, she began a long-term study of chromosome breakage and rejoining, and these studies ultimately brought her to the unanticipated discovery of transposable elements in the early 1940s. For over thirty years, she continued her work on transposable elements, illuminating their abilities to restructure the genome and alter the control of gene expression [6]. As she distributed her stocks to scientists for molecular analysis of the different transposons, she was fond of saying, 'They'll be amazed when they learn what they can do.'

It is not yet possible for us to evaluate the full significance of Barbara McClintock's scientific accomplishments. It is widely recognized that her work on transposable elements revolutionized our thinking about genome stability and genome reorganization. The Fluid Genome has replaced the Constant Genome. But her observations that cells can rapidly detect the presence of broken chromosomes and efficiently repair the breaks are still not well known, and their implications for the cell biology of heredity and for evolution remain to be fully explored[7]. Likewise, genetic theory has not yet fully incoporated McClintock's discovery of 'controlling elements,' repetitive mobile genetic systems that can alter the developmental expression of any genetic locus and can create control networks involving unlinked loci [8, 9].

There are two reasons that McClintock's insights are still outside the mainstream. The first is the common misconception that McClintock thought of controlling element insertions and excisions as the chief mechanism of developmental gene regulation. Her thinking was far more sophisticated. Although excisions could occur in a regulated manner and thereby create patterns, she also documented many novel patterns of gene expression that did not involve mutational events [10, 11]. For McClintock, each new controlling element insertion or modification of a resident element created a novel genetic structure which brought the affected locus under the control of a wide repertoire of regulatory mechanisms. The second obstacle to broad acceptance of McClintock's perspective is that standard theories are still framed in terms of independent genetic units, whereas McClintock thought of the genome as a complex unified system exquisitely integrated into the cell and the organism. While her experimental prowess made her one of science's great dissectors and while she had expert knowledge of hierarchical organization in biological systems, McClintock was also keenly aware of the basic interconnectedness of natural phenomena – what she used to call the 'oneness' of each genome, cell or organism. There is good reason to believe that McClintock's integral view of the genome will prove to be prophetic. Like controlling elements, molecular studies have also led us to appreciate the mosaic structure of individual genetic loci and the interactive nature of the genome. Thus, both molecular biology and McClintock's insightful method of analysis have carried the science of genetics into a new conceptual universe, one as different from classical genetics as quantum physics is from classical physics.

Perhaps McClintock's most challenging idea is the concept of 'smart cells,' a phrase she slipped in humorously at the end of her lectures in recent years. Behind this concept lay decades of experience. Her own work traced the development of tens of thousands of maize plants in intimate detail, and she avidly absorbed the work of other scientists, ranging from pioneers like Driesch and E.B. Wilson up to contemporary molecular cell biologists. She was deeply impressed by the ability of cells to sense internal and external cues, evaluate them, and respond with actions appropriate for survival and morphogenesis. How this monitoring and decision

making operate was, she felt, a key area for future exploration.

How did McClintock achieve so much? Her accomplishments would be astonishing under the best circumstances, but she worked in the context of prejudice against women and, for much of her career, in the face of general incomprehension. The answer lies in her complete intellectual freedom. Many scientists have been upset because Barbara McClintock characterized herself as a mystic. But this characterization was central to her creative genius as a scientist. To her, the term mystic did not mean someone who mystifies. Instead, for Barbara McClintock, a mystic was someone with a deep awareness of the mysteries posed by natural phenomena. The courage to say, 'I do not understand,' and the courage to investigate the unexplainable were at the heart of her remarkable success.

Barbara McClintock occupies a unique place in the history of biology. Her work spanned almost the entire 20th century. She began her studies only two decades after the rediscovery of Mendelism, and she was keenly aware of the fundamental contributions made by the 19th century naturalists, embryologists and cell biologists. She participated in many aspects of this century's revolutionary exploration into the physical basis of heredity, and her discoveries on genetic networks and genome reorganization have defined problems to be addressed in the 21st century. One day, she may well be seen as the key figure in 20th century biology. Barbara McClintock's life was long, and she has left us a rich scientific legacy that will reward continued study for decades to come.

## References

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